

Exhibit A



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
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Washington, D.C. 20231

US APPLICATION NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
07/971,857	JOHN	A-57832/WHDP

FLEHR, HOHBACH, TEST
ALBRITTON & HERBERT
FOUR EMBARCADERO CENTER
SAN FRANCISCO, CA 94111

INTERNATIONAL APPLICATION NO.

PCT/GB91/01134

I.A. FILING DATE

PRIORITY DATE

10 Jul. 1991 10 Jul. 1990

DATE MAILED: 31 March 1994

**NOTIFICATION OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C. 371
AND 37 CFR 1.494 OR 1.495**

1. The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as ☐ a Designated Office (37 CFR 1.494), ☒ an Elected Office (37 CFR 1.495), has determined that the above identified international application has met the requirements of 35 U.S.C. 371, and is **ACCEPTED** for national patentability examination in the United States Patent and Trademark Office.

2. The United States Application Number assigned to the application is shown above and the relevant dates are:

8 JAN 1993
35 U.S.C. 102(e) DATE

8 JAN 1993
DATE OF RECEIPT OF
35 U.S.C. 371 REQUIREMENTS

3. ☒ A request for immediate examination under 35 U.S.C. 371(f) was received on 8 JAN 1993 and the application will be examined in turn.

4. The following items have been received:

- ☒ U.S. Basic National Fee.
- ☒ Copy of the international application in:
 - ☐ a non-English language.
 - ☒ English.
- ☐ Translation of the international application into English.
- ☒ Oath or Declaration of inventor(s) for DO/EO/US.
- ☐ Copy of Article 19 amendments. ☐ Translation of Article 19 amendments into English.
The Article 19 amendments ☐ have ☐ have not been entered.
- ☐ The International Preliminary Examination Report in English and its Annexes, if any.
- ☐ Translation of Annexes to the International Preliminary Examination Report into English.
The Annexes ☐ have ☐ have not been entered.
- ☒ Preliminary amendment(s) filed 8 JAN 1993 and _____
- ☐ Information Disclosure Statement(s) filed _____ and _____
- ☐ Assignment document.
- ☐ Power of Attorney and /or Change of Address.
- ☐ Substitute specification filed _____
- ☐ Verified Statement Claiming Small Entity Status.
- ☐ Priority Document.
- ☒ Copy of the Search Report ☒ and copies of the references cited therein.
- ☐ Other:

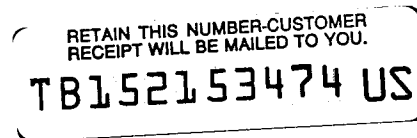
A Filing Receipt (PTO-103X) will be issued for the present application in due course. Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

Applicant is reminded that any communication to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above. (37 CFR 1.5)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:)
)
JOHN McCafferty, et al.)
)
Corresponding to:)
PCT/GB91/01134)
)
Serial No. Unknown)
)
Filed: Herewith)
)
For: METHODS FOR)
PRODUCING MEMBERS OF)
SPECIFIC BINDING PAIRS)
_____)

EXPRESS MAIL CERTIFICATE



Commissioner of Patents
and Trademarks
BOX PCT
Washington, DC 20231

CERTIFICATION UNDER 37 CFR §1.10

I hereby certify that this New Application and the documents listed below and referred to as enclosed herein are being deposited with the United States Postal Service on this date 8 January 1993 in an envelope bearing "Express Mail Post Office To Addressee" Mailing Label Number **TB152153474US** addressed to: Hon. Commissioner of Patents and Trademarks, Box PCT, Washington, D.C. 20231.

Vicki L. Henry
(person mailing)

Vicki L. Henry 8 Jan 93
Signature

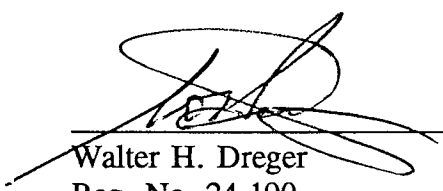
The following documents are enclosed herein for filing the above-identified new application:

1. Transmittal Letter to the U.S. Designated/Elected Office (in duplicate);

Serial No.: UNKNOWN
Filed: HERewith

2. Executed Declaration and Power of Attorney;
3. Copy of International Publication WO 92/01047;
4. Front Page of International Publication No. WO 92/01047;
5. International Search Report;
6. International Preliminary Examination Report;
7. Preliminary Amendment;
8. Check for \$2578.00 to cover the filing fee.

Dated: 8 January 1993



Walter H. Dreger
Reg. No. 24,190

FLEHR, HOHBACH, TEST, ALBRITTON & HERBERT
4 Embarcadero Center, Suite 3400
San Francisco, CA 94111
Telephone: (415) 781-1989

Dated: 8 January 1993

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)

A-57832/WHD

INTERNATIONAL APPLICATION NO.

PCT/GB91/01134

INTERNATIONAL FILING DATE

10 July 1991

PRIORITY DATE CLAIMED

10 Jul 90; 19
Oct 90; 12 Nov
90; 6 Mar 91; 15
May 91

TITLE OF INVENTION METHODS FOR PRODUCING MEMBERS OF SPECIFIC BINDING PAIRS

APPLICANT(S) FOR DO/EO/US McCafferty, John; POPE, Anthony; JOHNSON, Kevin; HOOGENBOOM, Hendricus;
GRIFFITHS, Andrew; JACKSON, Ronald; HOLLIGER, Kaspar; MARKS, James; CLACKSON, Timothy;
CHISWELL, David; WINTER, Gregory; BONNERT, Timothy

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items under 35 U.S.C. 371:

☒ This express request to immediately begin national examination procedures (35 U.S.C. 371(f)).2. ☒ The U.S. National Fee (35 U.S.C. 371(c)(1)) and other fees as follows:

CLAIMS	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
	TOTAL CLAIMS	60-20 =	40	x \$22.00	880.00
	INDEPENDENT CLAIMS	10-3 =	7	x \$74.00	518.00
	MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$230.00	230.00
	BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(4)):				
	<input type="checkbox"/> International preliminary examination fee paid to USPTO (37 CFR 1.482)				
 \$670				
	<input type="checkbox"/> No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))				
 \$710				
	<input checked="" type="checkbox"/> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(3)) paid to USPTO				
 \$950				950.00
	<input type="checkbox"/> International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2) to (4)				
 \$90				
	Surcharge of \$130. for furnishing the National fee or oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 mos. from the earliest claimed priority date (37 CFR 1.492(e)).				
	TOTAL OF ABOVE CALCULATIONS				2,578.00
	Reduction by 1/2 for filing by small entity, if applicable. Affidavit must be filed also. (Note 37 CFR 1.9, 1.27, 1.28.)				
	SUBTOTAL				
	Processing fee of \$130. for furnishing the English Translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 mos. from the earliest claimed priority date (37 CFR 1.492(f)).				
	TOTAL NATIONAL FEE				2,578.00
	Fee for recording the enclosed assignment (37 CFR 1.21(h)).				
	TOTAL FEES ENCLOSED				\$2,578.00

a. ☒ A check in the amount of \$2,578.00 to cover the above fees is enclosed.b. ☐ Please charge my Deposit Account No. 06-1300 in the amount of \$_____ to cover the above fees. A duplicate copy of this sheet is enclosed.c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-1300 (Order No. A-57832/WHD. A duplicate copy of this sheet is enclosed.

3. A copy of the International Application as filed (35 U.S.C. 371(c)(2))
- ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
 - ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
 - ☒ has been transmitted by the International Bureau.
4. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
5. Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
- ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - ☐ have been transmitted by the International Bureau.
6. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
7. ☒ An oath or declaration of the inventor (35 U.S.C. 371(c)(4)).
8. ☐ A translation of the Annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Other document(s) or information included:

9. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
10. ☐ An assignment document for recording.
Please mail the recorded assignment document to:
- ☐ the person whose signature, name and address appears at the bottom of this page.
 - ☐ the following:
11. The above checked items are being transmitted
- ☐ before the 18th month publication.
 - ☐ after publication and the Article 20 communication but before 20 months from the priority date.
 - ☐ after 20 months but before 22 months (surcharge and/or processing fee included).
 - ☐ after 22 months (surcharge and/or processing fee included).
Note: Petition to revive (37 CFR 1.137(a) or (b)) is necessary if 35 U.S.C. 371 requirements submitted after 22 months and no proper demand for International Preliminary Examination was made by 19 months from the earliest claimed priority date.
 - ☒ by 30 months and a proper demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
 - ☐ after 30 months but before 32 months and a proper demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date (surcharge and/or processing fee included).
 - ☐ after 32 months (surcharge and/or processing fee included).
Note: Petition to revive (37 CFR 1.137(a) or (b)) is necessary if 35 U.S.C. 371 requirements submitted after 32 months and a proper demand for International Preliminary Examination was made by 19 months from the earliest claimed priority date.
12. At the time of transmittal, the time limit for amending claims under Article 19
- ☐ has expired and no amendments were made.
 - ☐ has not yet expired.

13. ☐ Certain requirements under 35 U.S.C. 371 were previously submitted by the applicant on _____, namely:

14. _____ date
Preliminary Amendment, of the claims. (The fee calculations under Item 2. above for the claims reflect their status after entry of the preliminary amendment.)
15. International Preliminary Examination Report.

Walter H. Dreger - Flehr, Hohbach, Test, Albritton & Herbert
NAME

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ADDRESS

San Francisco, CA 94111

Tel: 415-781-1089 - Fax: 415-398-3249

Walter H. Dreger

24,190
REGISTRATION NUMBER

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled;

the specification of which

(check ☒ is attached hereto.
one)

☐ was filed on _____ as
Application Serial No. _____
and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
9015198.6	UK	10 JULY 1990	<input checked="" type="checkbox"/>	<input type="checkbox"/>
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
9022845.3	UK	19 OCTOBER 1990	<input checked="" type="checkbox"/>	<input type="checkbox"/>
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
9024503.6	UK	12 NOVEMBER 1990	<input checked="" type="checkbox"/>	<input type="checkbox"/>
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
9104744.9	UK	6 MARCH 1991	<input checked="" type="checkbox"/>	<input type="checkbox"/>
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
9110549.4	UK	15 MAY 1991	<input checked="" type="checkbox"/>	<input type="checkbox"/>
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
_____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulation, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
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(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
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I hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Harold C. Hohbach, Reg. No. 17,757; Aldo J. Test, Reg. No. 18,048; Thomas O. Herbert, Reg. No. 18,612; Donald M. MacIntosh, Reg. No. 20,316; Jerry G. Wright, Reg. No. 20,165; Edward S. Wright, Reg. No. 24,903; David J. Brezner, Reg. No. 24,774; Richard E. Backus, Reg. No. 22,701; James A. Sheridan, Reg. No. 25,435; Robert B. Chickering, Reg. No. 24,286; Willis E. Higgins, Reg. No. 23,025; Gary S. Williams, Reg. No. 31,066; Richard F. Trecartin, Reg. No. 31,801; Stephen C. Durant, Reg. No. 31,506; C. Michael Zimmerman, Reg. No. 20,451; Walter H. Dreger, Reg. No. 24,190; _____;

provided that if any one of said attorneys ceases being affiliated with the law firm of Flehr, Hohbach, Test, Albritton & Herbert as partner, employee or of counsel, such attorney's appointment as attorney and all powers derived therefrom shall terminate on the date such attorney ceases being so affiliated.

Direct all telephone calls to Walter H. Dreger at (415) 781-1989.

Address all correspondence to:

FLEHR, HOHBACH, TEST,
ALBRITTON & HERBERT
Suite 3400, Four Embarcadero Center
San Francisco, California 94111

File No. A-57832/WHD

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Title 18, United States Code, §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Exhibit B



US005969108A

United States Patent [19][11] **Patent Number:** **5,969,108****McCafferty et al.**[45] **Date of Patent:** **Oct. 19, 1999**[54] **METHODS FOR PRODUCING MEMBERS OF SPECIFIC BINDING PAIRS**

[75] Inventors: **John McCafferty**, Sawston; **Anthony Richard Pope**; **Kevin Stuart Johnson**, both of Cambridge; **Henricus Renerus Jacobus Mattheus Hoogenboom**, Little Shalford; **Andrew David Griffiths**, Cambridge; **Ronald Henry Jackson**, Cambridge; **Kaspar Philipp Holliger**, Cambridge; **James David Marks**, Cherry Hinton, all of United Kingdom; **Timothy Piers Clackson**, Palo Alto, Calif.; **David John Chiswell**, Middle Claydon, United Kingdom; **Gregory Paul Winter**; **Timothy Peter Bonnert**, both of Cambridge, United Kingdom

[73] Assignees: **Medical Research Council**, London; **Cambridge Antibody Technology Limited**, Cambridgeshire, both of United Kingdom

[21] Appl. No.: **07/971,857**[22] PCT Filed: **Jul. 10, 1991**[86] PCT No.: **PCT/GB91/01134**§ 371 Date: **Jan. 8, 1993**§ 102(c) Date: **Jan. 8, 1993**[87] PCT Pub. No.: **WO92/01047**PCT Pub. Date: **Jan. 23, 1992**[30] **Foreign Application Priority Data**

Jul. 10, 1990	[GB]	United Kingdom	9015198
Oct. 19, 1990	[GB]	United Kingdom	9022845
Nov. 12, 1990	[GB]	United Kingdom	9024503
Mar. 6, 1991	[GB]	United Kingdom	9104744
May 15, 1991	[GB]	United Kingdom	9110549

[51] **Int. Cl.⁶** **C07K 19/00**; C07H 21/04; C12N 15/13[52] **U.S. Cl.** **530/387.3**; 530/867; 435/9.1; 435/69.1; 435/69.8; 435/320.1; 435/235.1; 536/23.1; 536/23.53; 536/23.4[58] **Field of Search** 530/387.1, 412, 530/387.3, 867; 536/23.1, 23.53, 23.4; 435/5, 252.3, 6, 69.6, 7.1, 69.7, 9.1, 69.1, 69.8, 230.1, 320.1[56] **References Cited****U.S. PATENT DOCUMENTS**

4,593,002	6/1986	Dulbecco	435/172.3
4,816,397	3/1989	Boss et al.	435/68
4,946,778	8/1990	Ladner et al.	435/69.6
5,091,513	2/1992	Huston et al.	530/387
5,223,409	6/1993	Ladner et al.	435/69.7
5,403,484	4/1995	Ladner et al.	435/235.1
5,427,908	6/1995	Dower et al.	435/5

FOREIGN PATENT DOCUMENTS

B-27617/88 7/1989 Australia C12P 21/00

WO 83/02393	7/1983	WIPO	
WO 88/06630	9/1988	WIPO	C12P 21/00
WO 88/09344	12/1988	WIPO	C07K 13/00
WO 90/02809	3/1990	WIPO	C12P 21/00
WO 90/05144	5/1990	WIPO	C07K 13/00
WO 90/14424	11/1990	WIPO	C12N 15/00
WO 90/14430	11/1990	WIPO	C12P 19/34
WO 90/14443	11/1990	WIPO	C12Q 1/70
WO 91/10737	7/1991	WIPO	C12N 15/13
WO 91/17271	11/1991	WIPO	C12Q 1/70
WO 92/06204	4/1992	WIPO	C12N 15/64
WO 92/09690	6/1992	WIPO	C12N 15/00
WO 92/18619	10/1992	WIPO	C12N 7/01

OTHER PUBLICATIONSBass et al., *Proteins, Structure, Function and Genetics* 8:309-314 (1990).de la Cruz et al., *J. Biol. Chem.* 263(9):4318-4322 (1988).Huse et al., *Science* 246:1275-1281 (1989).Kang et al., *Proc. Natl. Acad. Sci. USA* 88:4363-4366 (1991).McCafferty et al., *Nature* 348:552-554 (1990).Milstein, F.R.S., *Proc. R. Soc. London B* 239:1-16 (1990).Parmley and Smith, *Gene* 73:305-318 (1988).Short et al., *Nucleic Acids Research* 16(15):7583-7600 (1988).Smith, *Science* 228:1315-1317 (1985).Tsunetsugu-Yokota et al., *Gene* 99:261-265 (1991).Winter and Milstein, *Nature* 349:293-299 (1991).

Kabat Sequences of Proteins of Immunological Interest 4th ed. (1987), p. 181.

Sambrook et al. *Molecular Cloning: A Laboratory Manual* 4.13, 4.14, 4.17-4.19, 4.46 and A.12 (1989).*Primary Examiner*—Frank C. Eisenschenk*Attorney, Agent, or Firm*—Marshall, O'Toole, Gerstein, Murray & Borun[57] **ABSTRACT**

A member of a specific binding pair (sbp) is identified by expressing DNA encoding a genetically diverse population of such sbp members in recombinant host cells in which the sbp members are displayed in functional form at the surface of a secreted recombinant genetic display package (rgdp) containing DNA encoding the sbp member or a polypeptide component thereof, by virtue of the sbp member or a polypeptide component thereof being expressed as a fusion with a capsid component of the rgdp. The displayed sbps may be selected by affinity with a complementary sbp member, and the DNA recovered from selected rgdps for expression of the selected sbp members. Antibody sbp members may be thus obtained, with the different chains thereof expressed, one fused to the capsid component and the other in free form for association with the fusion partner polypeptide. A phagemid may be used as an expression vector, with said capsid fusion helping to package the phagemid DNA. Using this method libraries of DNA encoding respective chains of such multimeric sbp members may be combined, thereby obtaining a much greater genetic diversity in the sbp members than could easily be obtained by conventional methods.

59 Claims, 46 Drawing Sheets